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Clinical Communications

New-onset asthma following COVID-19 in adults

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Clinical Implications

Our study suggests that a recent coronavirus disease 2019 (COVID-19) infection may rarely cause new-onset asthma, which could be linked to eosinophilic inflammation. Clinicians should consider asthma in the differential diagnosis of subacute or chronic respiratory symptoms following COVID-19 infection.

Viral infections, including respiratory syncytial virus, rhinovirus, and human metapneumovirus, have been suggested to elevate the risk for the development of incident asthma in children.[1,2] Although the relationship between viral infection and new-onset asthma in adults has not been extensively investigated, there have been reports that lower respiratory infections are related to new adult-onset asthma.[3] The risk of new asthma onset was strongly increased in adult patients who had experienced lower respiratory infections in the preceding 12 months,[3] suggesting a causal relationship between viral infection and new adult-onset asthma.

It is well known that some patients with coronavirus disease 2019 (COVID-19) have persistent respiratory symptoms (including coughing, dyspnea, or wheezing) even after the viral infection has subsided.[4] However, the development of new-onset asthma after COVID-19 has not been evaluated, even though these respiratory symptoms are very common in asthma. Therefore, we aimed to evaluate whether prior COVID-19 infection was associated with the new development of asthma. Previous COVID-19 diagnosis was determined by the patient's report of previous COVID-19 diagnosis based on the reverse-transcription polymerase chain reaction or antigen test. This study was approved by the institutional review board of our hospital (approval no.: HYUH-2022-11-056).

Between April 1, 2022, and October 30, 2022, 394 patients who had recovered from the acute phase of COVID-19 (at least 7 days after initial diagnosis) visited the pulmonology and allergy outpatient clinic due to respiratory symptoms (eg, coughing, dyspnea, sputum, or wheezing). Of these, 36 patients (9.1%) were suspected of having asthma. After excluding 16 patients diagnosed with asthma before COVID-19 and 3 patients with symptoms suspicious of asthma (eg, wheezing episodes) before COVID-19 infection, we identified 17 people (4.3%) with possible new asthma diagnosis after COVID-19 infection. Of these, 6 patients (1.5%) were confirmed to have asthma using the current diagnostic criteria of asthma.[5] For comparison, we also evaluated the proportion and odds of developing new-onset asthma in patients with no prior COVID-19 infection who were seen in our clinics during the same time frame. Analysis of a matched 1:3 cohort (n = 1,182) by age and sex, showed that COVID-19 infection was associated with higher odds of developing new-onset asthma (odds ratio 4.55; 95% CI 1.29−17.89).

Out of the 6 patients with newly diagnosed asthma after COVID-19, 3 were female and their ages ranged from 24 to 71 years. During the acute phase of COVID-19 infection, none of these patients required hospitalization for COVID-19 infection. The time between the COVID-19 and asthma diagnoses ranged from 27 to 271 days. All patients reported steadily worsening respiratory symptoms after COVID-19 infection. The most common symptoms were coughing (n = 6; 100%), followed by sputum production (n = 5; 83.3%), wheezing (n = 5; 83.3%), and dyspnea (n = 3; 50.0%) (Table I). Four patients were diagnosed with asthma based on methacholine provocation testing (MBPT) (a provocation concentration causing a 20% fall in the forced expiratory volume in 1 second [FEV_1] from the normal range of 0.77−13.13 mg/mL), and 2 patients were diagnosed with asthma based on documented excessive variability of lung function (ie, a variation in the $FEV_1 > 12\%$ and > 200 mL between visits in the absence of respiratory infection). Except for 1 patient who had airflow obstruction (postbronchodilator FEV_1/forced vital capacity < 0.7 as well as lower limit of normal value), all patients had a normal range of spirometry results. Of 3 patients who had total immunoglobulin E results, 1 had a total immunoglobulin E level greater than 100 IU/mL. Of the 5 patients who underwent environmental skin prick testing or multiple allergen simultaneous testing (AdvanSureTMAlloScreen, LG Chem), 1 patient was sensitized to *Dermatophagoides pteronyssinus* and *D. farinae*. Blood eosinophil counts at the time of asthma diagnosis were elevated in all patients (range 297−1,219 cells/μL), and the fractional exhaled nitric oxide level was increased (>20 ppb) in 4 out of 5 patients (Table II). All patients were treated with a medium- or high-dose inhaled corticosteroid/long-acting beta-2 agonist either with or without systemic corticosteroids, and symptoms were substantially improved in all patients.

In the era of the COVID-19 pandemic, most studies have focused on the relationship between COVID-19 and the risk of severe COVID-19 in patients with asthma. However, although still struggling with COVID-19 infection, we are now entering the post-COVID-19 era, and many post-COVID-19 patients suffer from respiratory symptoms that mimic asthma. Accordingly, more information is needed on whether COVID-19 infection can trigger new-onset asthma. In our study, all patients reported coughing as their main complaint. Long COVID-19 syndrome involves a variety of new or ongoing symptoms that people experience more than 4 weeks after developing a COVID-19 infection.[6] Considering that asthma usually presents as a chronic cough, it is interesting that our patients visited the clinic complaining of persistent coughing, which can be considered a symptom of long COVID-19. In our study, 5 patients with coughing also reported wheezing, so we easily suspected asthma. However, 1 had no wheezing, which made it difficult to

TABLE I. Clinical characteristics and treatment of patients with new-onset asthma following COVID-19 infection

Case number	1*	2	3*	4	5	6
Ethnicity	Asian	Asian	Asian	Asian	Asian	Asian
Age, y	71	36	46	24	58	56
Sex	Male	Female	Female	Male	Female	Male
Body mass index, kg/m^2	20.3	24.1	21.6	31.0	32.4	22.0
Smoking history	Nonsmoker	Nonsmoker	Nonsmoker	Smoker	Nonsmoker	Nonsmoker
Date of COVID-19 diagnosis	August 15, 2021	March5, 2022	March 21, 2022	April 1, 2022	April 1, 2022	May 15, 2022
Date of asthma diagnosis	May 13, 2022	April 7, 2022	July 25, 2022-	May 13, 2022	April 28, 2022	November 18, 2022
Time from the COVID-19 diagnosis to the asthma diagnosis, d	271	33	126	42	27	187
Comorbidities						
COPD	No	No	No	No	No	No
Tuberculosis	Yes	No	No	No	No	No
Previous allergic diseases	None	None	Allergic rhinitis	Allergic rhinitis	None	Allergic rhinitis
Respiratory symptoms						
Coughing	Yes	Yes	Yes	Yes	Yes	Yes
Wheezing	Yes	No	Yes	Yes	Yes	Yes
Dyspnea	Yes	No	Yes	Yes	No	No
Sputum	Yes	Yes	Yes	Yes	No	Yes
Treatment						
Inhaler	High-dose ICS/LABA	Medium-dose ICS/LABA	Medium-dose ICS/LABA	Medium-dose ICS/LABA	High-dose ICS/LABA	Medium-dose ICS/LABA
Systemic CS	Yes, intravenous mPD 62.5 mg for 2 d and then oral PD 40 mg for 3 d	No	No	Yes,Oral PD 40 mg for 7 d	No	No

COPD, Chronic obstructive pulmonary disease; *CS,* corticosteroid; *ICS,* inhaled corticosteroid; *LABA,* long-acting beta-2 agonist; *mPD,* methylprednisolone; *PD,* prednisolone.

*Patients 1 and 3 were diagnosed with asthma by a documented excessive variability in lung function variation in $FEV_1 > 12\%$ and > 200 mL between visits, in the absence of respiratory infections.

TABLE II. Result of laboratory tests in patients with new-onset asthma following COVID-19 infection

Case number	1	2	3	4	5	6
LLN of FEV_1/FVC*	61.7	76.0	73.4	78.3	70.6	66.5
LLL of FEV_1, L†	1.57	2.29	2.06	3.56	1.64	2.32
Spirometry during study period, n	3	1	4	4	3	2
Baseline spirometry‡						
FEV_1/FVC %	41.7	75.3	73.4	78.3	78.7	67.4
FEV_1, L	1.03	2.49	2.07	3.74	1.92	3.63
FEV_1%pred	31.9	79.2	68.5	83.8	84.4	93.9
Post-BD FEV_1/FVC	42.4	80.7	76.5	83.2	79.2	73.3
Post-BD FEV_1, L	1.08	2.55	2.27	4.11	1.99	3.94
Post-BD FEV_1%pred	33.7	81.1	75.1	91.9	87.1	101.9
Post-treatment spirometry						
FEV_1/FVC	69.5	NA	84.4	81.9	77.4	66.0
FEV_1, L	3.25	NA	2.65	4.13	1.79	3.55
FEV_1%pred	101.2	NA	86.7	92.6	78.5	91.9
Post-BD FEV_1/FVC	71.1	NA	87.0	83.3	80.3	72.4
Post-BD FEV_1, L	3.32	NA	2.64	4.33	1.86	3.80
Post-BD FEV_1%pred	103.6	NA	86.5	96.9	81.7	98.4
BDR	Negative	Negative	Negative	Negative	Negative	Negative
MBPT (PC_{20}, mg/mL)§	NA	Positive (7.17)	NA	Positive (10.08)	Positive (0.77)	Positive (13.13)
Baseline FeNO, ppb‡	156	NA	85	39	13	119
Posttreatment FeNO, ppb	58	NA	77	58	19	105
Baseline blood eosinophils, /uL	1219	597	585	297	510	393
Total IgE, IU/mL	NA	NA	NA	44.5	118.0	89.6
Skin prick test	Negative	NA	Negative	NA	Negative	NA
MAST	NA	NA	NA	Positive for DP and DF	NA	Negative

BD, Bronchodilator; *BDR,* bronchodilator response; *DP, Dermatophagoides pteronyssinus*; *DF, Dermatophagoides farina*; *FeNO,* fractional exhaled nitric oxide; *FVC,* forced vital capacity; *IgE,* immunoglobulin E; *LLN,* lower limit of normal; *MAST,* multiple allergen simultaneous test; *NA,* not available; *PC_{20},* provocation concentration causing a 20% fall in FEV_1; *%pred,* % predicted value

*The LLN for FEV_1/FVC was calculated for each subject using the new reference equations by Korean population. These were based on the predicted value − 1.645 × the standard error of the estimate.

†The LLN for FEV1 was calculated for the mean − 1.645 × the SD by spirometry data of Korean population according to the age groups.

‡The first tests were performed at the time of the first visit to the outpatient clinic owing to symptoms after COVID-19 infection.

§Positive MBPT was defined as $PC_{20} < 16$ mg/mL.

appropriately diagnose asthma. Further testing showed a positive MBPT. Although the latter case does not indicate that tests for asthma are mandatory when evaluating coughing after COVID-19, it might be helpful for physicians to recognize that cough-variant asthma can present similarly to long COVID-19 syndrome. If persistent coughing is not improved with symptom-relieving treatment, then asthma may be considered as 1 of the etiologies. Interestingly, in our study, only 1 patient had airflow obstruction, which may suggest that the absence of airflow obstruction cannot rule out post-COVID-19 asthma and also may indicate the important role of MBPT in the diagnosis of post-COVID asthma.

Our findings of elevated absolute eosinophil count and fractional exhaled nitric oxide in these patients with newly diagnosed asthma who responded well to inhaled corticosteroids with and without systemic steroids, along with minimal environmental allergens sensitization, indicate a T2-high nonallergic asthma phenotype. In line with our results, previous studies have shown that postviral inflammation in asthma is related to eosinophilic inflammation.[7] The exact mechanism that underlies how COVID-19 infection leads to asthma and which patients are susceptible to asthma is not well understood; however, 1 study reported that COVID-19 patients also could exhibit eosinophil-mediated inflammation.[8]

In conclusion, our study suggests that recent COVID-19 infection may rarely cause asthma, which might be linked to eosinophilic inflammation. Clinicians should consider asthma in the differential diagnosis of subacute or chronic respiratory symptoms following COVID-19 infection.

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